PATENT SPECIFICATION

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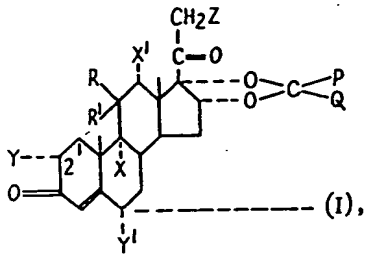
COMPLETE SPECIFICATION

Synthesis of Steroids

We, OLIN MATHIESON CHEMICAL CORPORATION, a Corporation organized and existing under the laws of the State of Virginia, United States of America, of 460, Park Avenue, New York 22, New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a method of preparing physiologically active steroids, and to the physiologically active steroids produced thereby.

The steroids of this invention include the 16α,17α-acetal and ketal derivatives of 16α,17α-dihydroxy steroids and ketones or aldehydes, and more particularly steroids of the general formula:

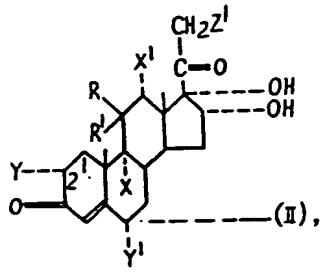


(I),

in which the 1- and 2- positions are saturated or double-bonded: R is hydrogen, R^1 is β-hydroxy or R and R^1 together constitute a keto group; X is hydrogen, halogen (i.e. fluoro, chloro, bromo or iodo), hydroxy, lower alkyl, or lower alkoxy; X^1 is hydrogen or lower alkyl; Y is hydrogen or methyl; Y^1 is halogen (preferably fluoro); Z is hydrogen, hydroxy or acyloxy (particularly the acyloxy radical of a hydrocarbon carboxylic acid of less than ten carbon atoms); and P and Q are hydrogen, lower alkyl, halogenated lower alkyl, monocyclic cycloalkyl, monocyclic aryl, monocyclic aryl lower alkyl, monocyclic heterocyclic, or monocyclic heterocyclic lower alkyl; or, together with the carbon atom to which they are joined, P and Q form a cycloalkyl or monocyclic heterocyclic group.

The term "lower" as and in the expressions "lower alkyl", "lower alkoxy" and "lower alkylene" throughout the description and claims refers to a radical with not more than 7 carbon atoms.

The compounds of this invention are prepared, in accordance with one process of this invention, by interacting a steroid reactant of the general formula:



(II),

in which the 1- and 2- positions are saturated or linked by a double bond; R, R^1, X, X^1, Y and Y^1 are as hereinbefore defined; and Z^1 is hydrogen or hydroxy, with an aldehyde or ketone of the formula: $O=C<^{P}_{Q}$, in which P and Q are as hereinbefore defined, and recovering the resultant acetal or ketal derivative, and, if desired, acylating the 21-hydroxy group with an acylhalide or an acid anhydride. The reaction is preferably carried out by treating a suspension or solution of the steroid in the aldehyde or ketone with or without an inert organic solvent (e.g. dioxan) with an acid catalyst (e.g. perchloric acid, *p*-toluenesulfonic acid and hydrochloric acid), neutralizing the acid and recovering the acetal or ketal derivative formed.

Among the suitable starting steroids utiliz-

[*Price 4s. 6d.*]

able in the process of this invention may be mentioned, 6α-halo-16α-hydroxyhydrocortisone (e.g. 6α - fluoro - 16α - hydroxyhydrocortisone), 6α - halo - 16α - hydroxycortisone, 6α-halo - 16α - hydroxyprednisolone, 6α - halo-16α - hydroxyprednisone, 6α,9α - dihalo-16α - hydroxyhydrocortisone (e.g. 6α,9α-difluoro - 16α - hydroxyhydrocortisone), 6α,9α - dihalo - 16α - hydroxycortisone, 6α,9α-dihalo - 16α - hydroxyprednisolone (e.g. 6α,9α - difluoro - 16α - hydroxyprednisolone), 6α,9α - dihalo - 16α - hydroxyprednisone, 2α-methyl - 6α - fluoro - 16α - hydroxyhydrocortisone, 2α - methyl - 6α - fluoro - 16α-hydroxycortisone, 6α - fluoro - 11β,16α,17α-trihydroxyprogesterone, 6α - fluoro - 11-keto - 16α,17α - dihydroxyprogesterone, 6α-fluoro - 11β,16α,17α - trihydroxy - 1 - dehydroprogesterone, 6α - fluoro - 11 - keto-16α,17α - dihydroxy - 1 - dehydroprogesterone, 6α,9α - dihalo - 11β,16α,17α - trihydroxyprogesterone (e.g. 6α,9α - difluoro-11β,16α,17α - trihydroxyprogesterone, 6α,9α-dihalo - 11β,16α,17α - trihydroxy - 1 - dehydroprogesterone (e.g. 6α,9α - difluoro-11β,16α,17α - trihydroxy - 1 - dihydroprogesterone), 6α - halo - 9α - (lower alkyl) - 16α-hydroxyhydrocortisone (e.g. 6α - fluoro - 9α-methyl - 16α - hydroxyhydrocortisone), 6α-halo - 9α - (lower alkyl) - 16α - hydroxycortisone, 6α - halo - 9α - (lower alkyl) - 16α-hydroxyprednisolone,6α - halo - 9α - (lower alkyl) - 16α - hydroxyprednisone, 6α,9α-dihalo - 12α - (lower alkyl) - 16α - hydroxyhydrocortisone (e.g. 6α,9α - difluoro - 12α-methyl - 16α - hydroxyhydrocortisone), 6α,9α-dihalo - 12α - (lower alkyl) - 16α - hydroxycortisone, 6α,9α - dihalo - 12α - (lower alkyl)-16α - hydroxyprednisolone (e.g. 6α - chloro-9α - fluoro - 12α - methyl - 16α - hydroxyprednisolone), and 6α,9α - dihalo - 12α-(lower alkyl)-16α-hydroxyprednisone.

Particularly preferred steroid reactants are those wherein the 1,2-position is either saturated or double-bonded, R is hydrogen, R^1 is β-hydroxy or together R and R^1 is keto; X is hydrogen, chlorine or fluorine; Y is hydrogen; Y^1 is fluoro; and Z^1 is hydrogen or hydroxy.

In those cases where the starting steroid reactants are new compounds, they can be prepared from the corresponding 16-desoxy derivative by subjecting the latter to the oxygenating action of a suitable microorganism such as *Streptomyces roseochromogenus*.

Suitable aldehyde and ketone reactants include aldehydes such as paraldehyde, propanal, chloral, hydrate, trifluoroacetaldehyde hemiacetal, heptafluorobutanal ethyl hemiacetal and hexanal; di(lower alkyl)ketones, such as acetone, diethylketone, dibutylketone, methylethylketone, and methylisobutylketone; mono and dicycloalkyl ketones, such as cyclohexylmethyl ketone and dicyclopropyl ketone; cycloalkanones, such as cyclobutanone, cyclopentanone, cyclohexanone, suberone, and cyclodexanone; monocyclic aromatic aldehydes such as benzaldehyde, halobenzaldehydes (e.g. *p*-chlorobenzaldehyde and *p*-fluorobenzaldehyde), lower alkoxy benzaldehydes (e.g. *o*-anisaldehyde), di(lower alkoxy) benzaldehydes (e.g. veratraldehyde), hydroxybenzaldehydes (e.g. salicylaldehyde), dihydroxy-benzaldehydes (e.g. resorcylaldehyde), lower alkyl benzaldehydes (e.g. *m*-tolualdehyde and *p* - ethylbenzaldehyde), di(lower alkyl) benzaldehydes (e.g. *o,p*-dimethylbenzaldehyde), nitrobenzaldehydes, acylamidobenzaldehydes (e.g. N - acetylanthranilaldehyde), and cyanobenzaldehydes; monocyclic aromatic lower alkanals, such as phenylacetaldehyde, α - phenyl-propionaldehyde, β - phenylpropionaldehyde, γ - phenylbutyraldehyde, and aromatically-substituted halo, lower alkoxy, hydroxy, lower alkyl, nitro, acylamido and cyano derivatives thereof; monocyclic heterocyclic aldehydes, such as picolinaldehydes, furfural, thiophene carbonals, and halo, lower alkoxy, hydroxy, lower alkyl, nitro, and cyano derivatives thereof; and monocyclic heterocyclic lower alkanals, monocyclic aromatic ketones, such as acetophenone, propiophenone, butyrophenone, valerophenone, isocaprophenone halophenyl lower alkyl ketones (e.g. *p*-chloroacetophenone and *p*-chloropropiophenone), (lower alkoxy)phenyl lower alkyl ketones (e.g. *p*-anisyl methyl ketone), di(lower alkoxy)-phenyl lower alkyl ketones, hydroxyphenyl lower alkyl ketones, dihydroxyphenyl lower alkyl ketones (e.g. resacetophenone), (lower alkyl)phenyl lower alkyl ketones (e.g. methyl *p*-tolyl ketone), di(lower alkyl)phenyl lower alkyl ketones (*o,p*-xylyl methyl ketone), nitrophenyl lower alkyl ketones (e.g. *p*-nitroacetophenone), acylamidophenyl lower alkyl ketones (e.g. acetylanilines), and cyanophenyl lower alkyl ketones; benzophenone, and mono or bis substituted halo, lower alkoxy, hydroxy, lower alkyl, nitro, acylamido and cyano derivatives thereof; monocyclic aromatic lower alkanones, such as 1-phenyl-3-butanone and 1-phenyl-4-pentanone, and aromatically substituted derivatives thereof; monocyclic heterocyclic ketones, such as 2-acetyl-furan, 2-benzoyl furan, and 2-acetylthiophene; monocyclic heterocyclic lower alkanones; and monocyclic heterocyclic ketones, such as alloxane.

If a 21-ester derivative is the desired product, the corresponding 21-hydroxy steroid can be acylated in the usual manner, e.g. by treatment with an acyl halide or acid anhydride. Thus, to prepare the preferred 21-acyloxy derivatives wherein the acyl radical corresponds to the acyl radical of a hydrocarbon carboxylic acid of less than ten carbon atoms, either the acyl halide or acid anhydride of a lower alkanoic acid (e.g. acetic, propionic and tertbutyric acid), a monocyclic aryl car-

boxylic acid (e.g. benzoic and toluic acid), a monocyclic aryl lower alkanoic acid (e.g. phenacetic and β-phenylpropionic acid), a lower alkanoic acid, a cycloalkanecarboxylic acid, or a cycloalkenecarboxylic acid is employed as a reactant.

All of the compounds of this invention are physiologically - active substances which possess glucocorticoid and anti-inflammatory activity and hence can be used in lieu of known glucocorticoids such as hydrocortisone and cortisone in the treatment of rheumatoid arthritis, in the treatment of dermatoses, for which purpose they can be administered in the same manner as hydrocortisone, for example, the dosage being adjusted for the relative potency of the particular steroid.

The following examples are illustrative of the invention (all temperatures being in Centigrade):

EXAMPLE 1.

16α,17α - Isopropylidene 6α - Fluoro - triamcinolone (16α,17α - Isopropylidene-6α,9α - difluoro - $\Delta^{1,4}$ - pregnadiene-11β,16α,17α,21-tetrol-3,20-dione)

To a suspension of 500 mg. of 6α-fluoro-triamcinolone in 75 ml. of acetone is added 0.05 ml. of 72% perchloric acid and the mixture agitated at room temperature for three hours. During this period the crystals gradually dissolve and the clear solution is neutralized with dilute bicarbonate and the acetone removed *in vacuo*. The resulting crystalline suspension is filtered and the crystals washed with water. The dried material is recrystallized from 95% alcohol to give the desired pure acetonide.

EXAMPLE 2.

To a suspension of 500 mg. of 6α-fluoro-triamcinolone in 75 ml. of acetone is added 0.05 ml. of concentrated hydrochloric acid and the mixture is stirred at room temperature for 6 hours. It is then treated as described in Example 1 and gives the same pure 6α-fluoro-triamcinolone acetonide.

EXAMPLE 3.

A suspension containing 100 mg. of 6α-fluoro-triamcinolone and 50 mg. of *p*-toluenesulfonic acid in 15 ml. of acetone is stirred for 21 hours at room temperature. The clear solution is worked up as described in Example 1 to give the same pure acetonide.

EXAMPLE 4.

16α,17α - Isopropylidene 6α - Fluoro - triamcinolone 21-Acetate

A solution of 50 mg. of the 6α-fluoro-triamcinolone acetonide described in Example 1 in 1 ml. of pyridine and 1 ml. of acetic anhydride is allowed to stand at room temperature for 18 hours. Removal of the reagents *in vacuo* gives a crystalline residue which after crystallization from acetone-hexane gives the desired pure 21-acetate.

EXAMPLE 5.

16α,17α - (2^1 - Butylidene) 6α - Fluoro-triamcinolone

To a suspension of 100 mg. of 6α-fluoro-triamcinolone in 15 ml. of methylethylketone is added 0.05 ml. of 72% perchloric acid, and the mixture stirred at room temperature for two hours. The resulting solution is neutralized with sodium bicarbonated solution and after addition of water the methylethylketone is evaporated *in vacuo*. The resulting crystals are filtered, washed with water and dried *in vacuo*. Recrystallization from acetone-hexane gives the desired pure isobutylidene derivative.

EXAMPLE 6.

16α,17α - (4^1 - Methyl - 2^1 - pentylidene) 6α-Fluoro-triamcinolone

To a suspension of 100 mg. of 6α-fluoro-triamcinolone in 15 ml. of methylisobutylketone is added 0.05 ml. of 72% perchloric acid. The mixture is stirred at room temperature for 6 hours and the resulting solution extracted with dilute sodium bicarbonate solution, washed with water, the organic phase dried over sodium sulfate and the solvent evaporated *in vacuo*. Recrystallization of the resulting crystals from acetone-hexane gives the desired pure isohexylidene derivative.

EXAMPLE 7.

16α,17α - Cyclohexylidene 6α - Fluoro-triamcinolone

A suspension of 200 mg. of 6α-fluoro-triamcinolone in 15 ml. of redistilled cyclohexanone is treated for two hours as described in Example 6 to form the desired cyclohexylidene.

EXAMPLE 8.

16α,17α - (3^1 - Pentylidene) 6α - Fluoro-triamcinolone

A suspension of 200 mg. of 6α-fluoro-triamcinolone in 30 ml. of diethylketone is treated for four hours as described in Example 6 to form the desired pentylidene.

EXAMPLE 9.

16α,17α-Ethylidene 6α-Fluoro-triamcinolone

To a suspension of 200 mg. 6α-fluoro-triamcinolone in 15 ml. of freshly distilled paraldehyde is added 0.05 ml. of 72% perchloric acid and the mixture agitated for 3.5 hours at room temperature. The resulting solution is extracted with dilute bicarbonate and water, dried and the excess paraldehyde removed *in vacuo*. The residual material represents 16α,17α-ethylidene 6α-fluoro-triamcinolone.

Substitution of 6α,9α-difluoro-$\Delta^{1,4}$-pregnadiene - 16α,17α - 21 - triol - 3,11,20 - trione for 6α-fluoro-triamcinolone in the procedures of Examples 1 through 9, yield the corresponding 11-keto derivatives.

EXAMPLE 10.

16α,17α - Isopropylidene 6α,9α - Difluoro-Δ^4 - pregnene - 11β,16α,17α,21 - tetrol-3,20-dione

A suspension of 200 mg. of 6α,9α-difluoro-Δ^4 - pregnene - 11β,16α,17α,21 - tetrol - 3,20-dione in 30 ml. of acetone is stirred at room temperature with 100 mg. of *p*-toluenesulfonic acid monohydrate for 18 hours. The clear solution is neutralized with sodium bicarbonate solution and the acetone evaporated *in vacuo*. The resulting crystals are filtered and dried *in vacuo*. Recrystallization from acetone-hexane gives the desired pure isopropylidene derivative.

Reaction of 6α,9α-difluoro-Δ^4-pregnene; 16α,17α,21-triol-3,11,20-trione with acetone gives the corresponding 11-keto derivative.

EXAMPLE 11.

16α,17α - Cyclohexylidene 6α - Fluoro - 16α-hydroxyhydrocortisone

To a suspension of 100 mg. of 6α-fluoro-16α-hydroxy-hydrocortisone in 15 ml. of cyclohexanone is added 0.05 ml. of 72% perchloric acid. The mixture is treated as in Example 6 and results in the formation of the 16α,17α-cyclohexylidene derivative of 6α-fluoro-16α-hydroxyhydrocortisone.

If 6α-fluoro-16α-hydroxycortisone is substituted for the 6α-fluoro-16α-hydroxyhydrocortisone in the procedure of Example 11, 16α,17α - cyclohexylidene 6α - fluoro - 16α-hydroxycortisone is obtained.

EXAMPLE 12.

16α,17α - Isopropylidene 6α - Fluoro - 16α-hydroxyprednisolone

Treatment of 6α-fluoro-16α-hydroxyprednisolone with acetone in the presence of perchloric acid according to the procedure of Example 1 results in the formation of 16α,17α-isopropylidene 6α-fluoro-16α-hydroxyprednisolone.

EXAMPLE 13.

16α,17α - Isopropylidene 6α - Fluoro - 9α-Methyl-16α-hydroxyprednisolone

a) Preparation of 5α,6α-Oxido-9α-Methylhydrocortisone 3,20-ethylene is Ketal:

To a solution of 750 mg. of 9α-methylhydrocortisone 3,20-bis-ethylene ketal in 50 ml. of chloroform is added at 0° 7.5 ml. of 0.28 N perbenzoic acid. After 18 hours at 4° the mixture is washed successively with sodium iodide, sodium bicarbonate, dilute sodium sulfite and water, the chloroform solution dried and the solvent removed *in vacuo*. The residual desired 5α,6α-epoxide is recrystallized from acetone-hexane.

b) Preparation of 6β-fluoro-9α-methylpregnane - 5α,11β,17α,21 - tetrol - 3,20 - dione 3,20-bis-ethylene ketal:

To a solution of 500 mg. of 5α,6α-epoxy-9α - methylhydrocortisone 3,20 - bisethylene ketal in 60 ml. of dry benzene and 15 ml. of absolute ether is added 1 ml. of freshly redistilled boron trifluoride etherate and the solution allowed to remain at room temperature for three hours. After thorough washing with water the organic phase is dried over sodium sulfate and the solvents removed *in vacuo*. Recrystallization from acetone-hexane gives the desired pure fluorohydrin.

c) Preparation of 6α-fluoro-9 -methylhydrocortisone:

To a solution of 500 mg. of 6β-fluoro-9α-methylpregnane - 5α - 11β,17α,21 - tetrol-3,20-dione 3,20-bis-ethylene ketal in 25 ml. of glacial acetic acid is added 3 ml. of concentrated hydrochloric acid, and the resulting solution allowed to remain at room temperature for 18 hours. The mixture is diluted with water and chloroform, the chloroform solution washed with water, dilute sodium bicarbonate and again with water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The resulting 6α-fluoro-9α-methylhydrocortisone is recrystallized from acetone-hexane.

d) Preparation of 6α-fluoro-9α-methyl-16α-hydroxyhydrocortisone:

6α - Fluoro - 9α - methylhydrocortisone is fermented with *Streptomyces roseochromogenus* (Waksman No. 3689) and the resultant 6α - fluoro - 9α - methyl - 16α - hydroxyhydrocortisone is extracted from the filtered broth with methylisobutyl ketone and recovered from the latter solvent by concentration and filtration of the resulting crystalline material.

e) Preparation of 6α-fluoro-9α-methyl-16α-hydroxyprednisolone:

6α - Fluoro - 9α - methyl - 16α - hydroxyhydrocortisone is dehydrogenated in a concentration of 200 ug./ml. with *Nocardia aurantia* microorganisms thereby yielding 6α-fluoro - 9α - methyl - 16α - hydroxyprednisolone.

f) Preparation of 16α,17α-isopropylidene 6α-fluoro - 9α - methyl - 16α - hydroxyprednisolone:

Following the procedure of Example 1, but substituting 500 mg. of 6-fluoro-9α-methyl-16α-hydroxyprednisolone for the 6α-fluorotriamcinolone in the Example, there is obtained 16α,17α - isopropylidene 6α - fluoro - 9α-methyl-16α-hydroxyprednisolone.

EXAMPLE 14.

16α,17α - Isopropylidene 6α,9α - Difluoro-12α - methyl - 16α - hydroxyhydrocortisone

a) Preparation of 9α-fluoro-12α-methylhydrocortisone 3,20-bis-ethylene ketal:

A mixture of 2 g. of 9α-fluoro-12α-methylhydrocortisone, 40 mg. of *p*-toluenesulfonic acid, 32 ml. of ethylene glycol and 60 ml. of benzene is heated at reflux with a Dean-Stark separator for six hours. After cooling, the mixture is neutralized with dilute sodium bicarbonate, the layers separated and the aqueous phase extracted with chloroform. The combined benzene and chloroform phases are washed with water, dried over sodium sulfate

and the solvents evaporated *in vacuo*. The residual diketal is recrystallized from acetone.

b) Preparation of 16α,17α-isopropylidene 6α, 9α - difluoro - 12α - methyl - 16α - hydroxy-hydrocortisone:

Following the procedures in steps *a, b, c, d,* and *f* of Example 13, but substituting 800 mg. of 9α-fluoro-12α-methylhydrocortisone 3,20-bis-ethylene ketal for the 9α-methyl-hydrocortisone 3,20-bis-ethylene ketal in step *a*, there is obtained 16α,17α-isopropylidene 6α,9α - difluoro - 12α - methyl - 16α - hydroxy-hydrocortisone.

EXAMPLE 15.

16α,17α - Isopropylidene 6α,9α - Difluoro-12α-methyl-16α-hydroxyprednisolone

Following the procedures in steps *e* and *f* of Example 13, but substituting 6α,9α-difluoro-12α - methyl - 16α - hydroxyhydrocortisone for the 6α-fluoro,9α-methyl-16α-hydroxy-hydrocortisone in step *e*, there is obtained 16α,17α - isopropylidene 6α,9α - difluoro-12α-methyl-16α-hydroxyprednisolone.

EXAMPLE 16.

16α,17α - Isopropylidene 6α,9α - Difluoro-$\Delta^{1,4}$ - pregnadiene - 11β,16α,17α - triol-3,20-dione

a) Preparation of 6α-fluorotriamcinolone acetonide 21-mesylate:

To a solution of 1.5 g. of 6α-fluorotriamcinolone acetonide in 15 ml. of anhydrous pyridine is added at 0° 1.5 ml. of methanesulfonyl chloride. After 2.5 hours in the refrigerator ice water is added and the resulting precipitate filtered off and washed thoroughly with water. The material is dried and used without further purification in the reduction step.

b) Preparation of 16α,17α-Isopropylidene 6α,9α - difluoro - $\Delta^{1,4}$ - pregnadiene - 11β, 16α,17α-triol-3,20-dione:

A solution of 500 mg. of the above mesylate and 1.5 gm. sodium iodide in 50 ml. of glacial acetic acid is refluxed for 4 hours. The solution is concentrated *in vacuo*, water is added and the steroids extracted with chloroform. The chloroform extract is washed with sodium bicarbonate solution and water, dried over sodium sulfate and the solvent evaporated to dryness *in vacuo*. The residual acetonide is recrystallized from acetone-hexane.

Replacing 6α-fluorotriamcinolone acetonide in example 16 by 6α,9α-difluoro-Δ^4-pregnene-11β,16α,17α,21 - tetrol - 3,20 - dione acetonide there is obtained the corresponding Δ^4-pregnene derivative.

EXAMPLE 17.

16α,17α-Chloral Derivative of 6α-Fluorotriamcinolone

A suspension of 500 mg. of 6α-fluorotriamcinolone and 4 gm. of chloral hydrate in 20 ml. of dioxan is agitated at room temperature for 24 hours. The mixture is filtered, neutralized with aqueous sodium bicarbonate and extracted with chloroform. The chloroform-dioxane phase is dried over sodium sulfate, the solvent removed *in vacuo* and the residual desired chloral derivative crystallized from methanol.

EXAMPLE 18.

16α17α - (1,1,1, - Trifluoroisopropylidene)-6α-fluorotriamcinolone

Following the procedure of Example 1 but replacing the 75 ml. acetone used in that example by a mixture of 10 ml. of dioxane and 10 ml. of 1,1,1,-trifluoroacetone there is obtained the desired trifluoroisopropylidene derivative.

EXAMPLE 19.

16α,17α-Acetophenone Derivative of 6α-Fluoro-triamcinolone

To a suspension of 4 g. of 6α-fluoro-triamcinolone in 100 ml. of freshly redistilled acetophenone is added 1.0 ml. of 72% perchloric acid and the mixture stirred at room temperature for two hours, during which period all the 6α-fluoro-triamcinolone has dissolved. The solution is neutralized by the addition of 8 ml. of 1.1 N NaOH and of sufficient aqueous bicarbonate to render it neutral. Water and chloroform is then added and the chloroform acetophenone layer concentrated in high vacuum. The residue is recrystallized from acetonehexane and the crystals of the desired derivative washed well with hexane to remove adhering acetophenone.

EXAMPLE 20.

16α,17α - *p* - Nitroacetophenone Derivative of 6α-Fluorotriamcinolone

To a suspension of 200 mg. of 6α-fluoro-triamcinolone in a mixture of 7 ml. of dioxan and 4 grams of *p*-nitroacetophenone is added 0.05 ml. of 72% perchloric acid and the mixture stirred at room temperature for 3½ hours. The mixture is then neutralized with dilute sodium bicarbonate solution and the dioxan and excess *p*-nitroacetophenone removed by vacuum steam distillation. The residual aqueous suspension is extracted with chloroform, the chloroform layer washed with water, dried over sodium sulfate and the solvent removed *in vacuo*. The remaining derivative is purified by recrystallization from acetone-hexane.

EXAMPLE 21.

16α,17α - Acetophenone Derivative of 6α-Fluorotriamcinolone 21-Acetate

A solution of 50 mg. of the 16α,17α-acetophenone derivative of 6α-fluorotriamcinolone in 1 ml. of pyridine and 1 ml. of acetic anhydride is allowed to stand at room temperature for 18 hours. Removal of the reagents *in vacuo* gives a crystalline residue which after crystallization from acetone-hexane gives the pure acetate.

Substitution of 6α,9α-difluoro-$\Delta^{1,4}$-pregnadiene - 16α,17α,21 - triol - 3,11,20 - trione for 6α-fluorotriamcinolone in the procedures of Examples 19 through 21, yield the corresponding 11-keto derivatives.

EXAMPLE 22.

16α,17α - Acetophenone Derivative of 6α,9α-Difluoro - Δ^4 - pregnene 11β,16α,17α,21-tetrol-3,20-dione

A suspension of 200 mg. of 6α,9α-difluoro-Δ^4 - pregnene - 11β,16α,17α,21 - tetrol - 3,20-dione in 30 ml. of acetophenone is stirred at room temperature with 100 mg. of *p*-toluenesulfonic acid monhydrate for 18 hours. The clear solution is neutralized with sodium bicarbonate solution and the acetone evaporated *in vacuo*. The resulting crystals are filtered and dried *in vacuo*. Recrystallization from acetone-hexane gives the pure acetophenone derivative.

Reaction of 6α,9α-difluoro-Δ^4-pregnene-16α,17α,21-triol-3,11,20-trione with acetophenone gives the corresponding 11-keto derivative.

EXAMPLE 23.

16α,17α - Benzaldehyde Derivative of 6α-Fluoro-16α-hydroxyhydrocortisone

To a suspension of 100 mg. of 6α-fluoro-16α-hydroxyhydrocortisone in 15 ml. of benzaldehyde is added 0.05 ml. of 72% perchloric acid. The mixture is treated as in Example 19 and results in the formation of the 16α,17α-benzaldehyde derivative of 6α-fluoro-16α-hydroxyhydrocortisone.

If 6α-fluoro-16α-hydroxycortisone is substituted for the 6α-fluoro-16α-hydroxyhydrocortisone in the procedure of Example 23 the 16α,17α-benzaldehyde derivative of 6α-fluoro-16α-hydroxycortisone is obtained.

EXAMPLE 24.

16α,17α-Furfural Derivative of 6α-Fluoro-16α-hydroxyprednisolone

Treatment of 6α-Fluoro-16α-hydroxyprednisolone with furfural in the presence of perchloric acid according to the procedure of Example 19 results in the formation of the 16α,17α-furfural derivative of 6α-fluoro-16α hydroxyprednisolone.

EXAMPLE 25.

16α,17α-Alloxane Derivative of 6α-Fluorotriamcinolone

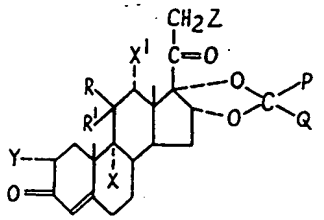
A suspension of 0.5 gm. 6α-fluorotriamcinolone and 2.5 gm. of alloxane in 20 ml. of dioxan and 0.15 ml. of 72% perchloric acid is agitated at room temperature for 24 hours. The mixture is neutralized with aqueous sodium bicarbonate solution and after the addition of 20 ml. of water extracted with chloroform. The chloroform extract is dried over sodium sulfate and evaporated to dryness *in vacuo*. The residual alloxane derivative is recrystallized from 95% alcohol.

EXAMPLE 26.

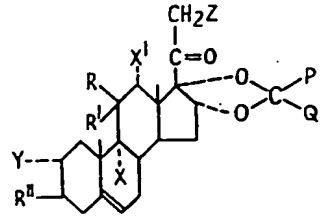
16α,17α-Dicyclopropyl Ketone Derivative of 6α-Fluorotriamcinolone

Following the procedure of Example 18 but replacing the trifluoroacetone by dicyclopropyl ketone, there is obtained the 16α,17α-dicyclopropyl derivative of 6α-fluorotriamcinolone.

The steroids of this invention can also be prepared by an alternative method which entails the interaction of a steroid of the general formula:

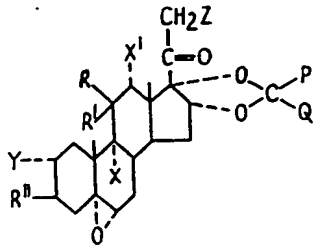


wherein R, R^1, X, X^1, Y, Z, P and Q are as hereinbefore defined, with a mono or dihydric alcohol, such as a lower alkanol or a lower alkanediol, such as ethanol, propanol, ethylene glycol or propylene glycol, to yield the corresponding 3-mono-ketal derivative of the formula



wherein, R, R^1, X, X^1, Y, Z, P and Q are as hereinbefore defined, and R^{11} is -O-(lower alkylene)-O- or two lower alkoxy radicals, the ketalization reaction is preferably conducted in the presence of a strong acid such as *p*-toluenesulfonic acid.

The 3-monoketal thus formed is then reacted with a peracid, such as perbenzoic acid or peracetic acid, to yield the 5α,6α-epoxy derivative of the formula



wherein R, R^1, R^{11}, X, X^1, Y, Z, P and Q are as hereinbefore defined.

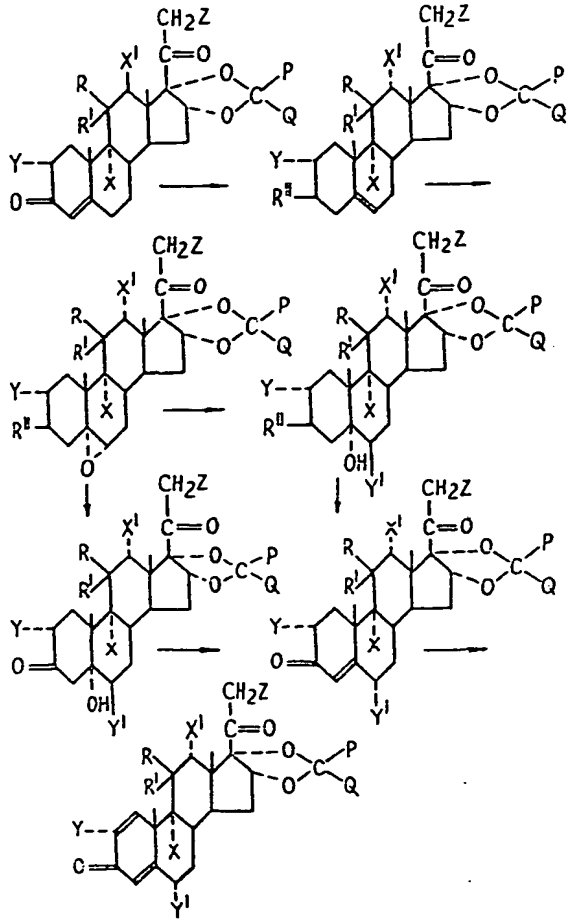
The 5α,6α-epoxy derivative is then treated with a hydrogen halide (i.e. hydrogen fluoride, hydrogen chloride, hydrogen bromide and hydrogen iodide) or boron trifluoride, to yield the corresponding 6β-halo-5α-hydroxy derivative, the reaction preferably being conducted in the cold (i.e. below room temperature) in an organic solvent for both the steroid and hydrogen halide reactant. If the reaction is carried out employing an aqueous solution of

the hydrogen halide, that is a hydrohalic acid, the 3-ketal group is hydrolyzed yielding the 3-keto-Δ^4-pregnene derivative.

The 5α-hydroxy-6β-halo derivative is then treated with a strong inorganic acid, e.g. perchloric acid or hydrochloric acid, preferably in glacial acetic acid, to invert the 6β-halo group and to dehydrate the steroid (with resulting hydrolysis of the 3-keto group, if not previously accomplished), thereby yielding the desired 6α-halo-3-keto-Δ^4-pregnene derivative.

If a $\Delta^{1,4}$-pregnadiene is desired as the product, the Δ^4-pregnene can then be subjected to microbial 1-dehydrogenation by using for example, the microorganisms *Nocardia aurantia*. Furthermore, if a 21-ester is desired and a free 21-hydroxy steroid is used as the reactant, the 21-hydroxy steroid formed can be esterified in the usual manner by treatment with an acyl halide or acid anhydride of a hydrocarbon carboxylic acid of less than ten carbon atoms as described hereinbefore.

The series of steps in the alternative process of this invention can be represented by the following equations:



The following Examples illustrate the alternative process of this invention (all temperatures being in Centigrade):

EXAMPLE 27.

9α - Fluoro - 16α - hydroxyhydrocortisone-16α,17α-Acetonide 3-Ethylene Ketal

A mixture of 2 grams of 9α-fluoro-16α-hydroxyhydrocortisone-16α,17α-acetonide, 40 mg. of *p*-toluenesulfonic acid, 16 ml. of ethylene glycol and 60 ml. of benzene is heated at reflux with a Dean-Stark separator for 6 hours. After cooling, the mixture is neutralized with dilute sodium bicarbonate, the layers are separated and the aqueous phase extracted with chloroform. The combined benzene and chloroform phases are washed with water, dried over sodium sulfate and the solvents evaporated *in vacuo*. The residual desired ketal after recrystallization from acetone has the following properties: m.p. about 248—250°, $[\alpha]_D^{23} + 1.5°$ (c,0.51 in $CHCl_3$); λ_{max}^{Nujol} 2.93, 5.86μ. Nujol is a Registered Trade Mark.

5α,6α - Oxido - 9α - fluoro - 16α - hydroxyhydrocortisone 16α,17α - Acetonide 3-Ethylene Ketal

To a solution of 1 gm. of 9α-fluoro-16α-hydroxyhydrocortisone 16α,17α-acetonide 3-ethylene ketal in 20 ml. of chloroform is added an ice-cold solution of 0.4 gm. of perbenzoic acid in 10 ml. of chloroform. After 18 hours at 4° the mixture is washed with dilute sodium bicarbonate and water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residual desired epoxide is crystallized from acetone-hexane.

6β - Chloro - 9α - fluoropregnane - 5α,11β,-16α,17α,21 - pentol - 3,20 - dione Acetonide 3-Ethylene Ketal

To a solution of 500 mg. of 5α,6α-oxido-9α - fluoro - 16α - hydroxyhydrocortisone-16α,17α-acetonide 3-ethylene ketal in 50 ml. of ice-cold chloroform is added 7 ml. of an ice-cold 0.5 N solution of hydrogen chloride in chloroform. The mixture is allowed to remain at 0° for two hours, after which it is washed with dilute sodium bicarbonate solution and water. The chloroform solution is dried over sodium sulfate and the solvent evaporated *in vacuo*. The residual chlorohydrin is used without further purification.

6α - Chloro - 9α - fluoro - 16α - hydroxyhydrocortisone-16α,17α-Acetonide

To a solution of 500 mg. of the chlorohydrin obtained above in 25 ml. of glacial acetic acid is added 3 ml. of concentrated hydrochloric acid, and the resulting solution allowed to remain at room temperature for

18 hours. The mixture is diluted with water and chloroform, the chloroform solution washed with water, dilute sodium bicarbonate and again with water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The resulting 6α - chloro - 9α - fluoro - 16α-hydroxyhydrocortisone - 16α,17α - acetonide is recrystallized from acetone-hexane.

EXAMPLE 28.

6α - Chloro - 9α - fluoro - 16α - hydroxyprednisolone-16α,17α-Acetonide

6α - Chloro - 9α - fluoro - 16α - hydroxyhydrocortisone-16α,17α-acetonide is dehydrogenated in a concentration of 200 ug./ml. with *Nocardia aurantia* microorganisms.

Instead of the anhydrous hydrogen chloride used in Example 27 in the opening of the 5α,6α-epoxide, aqueous hydrochloric acid can be used as follows. In this case the 3-ethylene ketal is hydrolyzed.

EXAMPLE 29.

6β - Chloro - 9α - fluoropregnane - 5α,11β,-16α,17α,21-pentol-3,20-dione Acetonide

To a solution of 500 mg. of 5α,6α-oxido-9α - fluoro - 16α - hydroxyhydrocortisone-16α,17α-acetonide 3-ethylene ketal in 20 ml. of dioxan is added 2 ml. of concentrated hydrochloric acid and the mixture allowed to stand at room temperature for two hours. Chloroform is then added and the mixture extracted with water, dilute sodium bicarbonate and again with water. The chloroform-dioxan phase is dried over sodium sulfate and the solvents removed *in vacuo*. The residual chlorohydrin is recrystallized from acetone-hexane.

Replacing the hydrochloric acid in Examples 27 or 29 by hydrobromic or hydroiodic acid results in the formation of the corresponding 6β-bromo and 6β-iodo-derivatives, which can be converted to 6α-bromo-9α-fluoro - 16 - hydroxyhydrocortisone - 16α,17α-acetonide and 6α - iodo - 9α - fluoro - 16α-hydroxyhydrocortisone - 16α,17α - acetonide, respectively, by the process of Example 27.

6β,9α - Difluoro - pregnane - 5α,11β,16α,17α-21-pentol-3,20-dione-16α,17α-Acetonide

To a solution of 500 mg. of 5α,6α-oxido-9α - fluoro - 16α - hydroxyhydrocortisone-16α,17α-acetonide 3-ethylene ketal in 25 ml. of chloroform is added 5 ml. of 48% aqueous hydrofluoric acid and the mixture agitated at room temperature for one hour. Water and chloroform is added and the mixture neutralized with sodium bicarbonate. The chloroform layer is dried over sodium sulfate and the solvent removed *in vacuo*. The residual 6β-fluorohydrin is recrystallized from acetone-hexane.

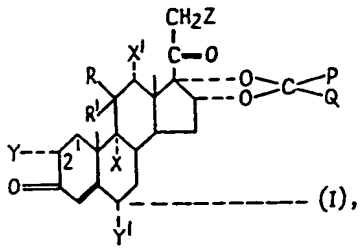
The 6β-fluorohydrin is converted into 6α,9α - difluoro - 16α - hydroxyhydrocortisone acetonide as described in Example 27 for the 6β-chloro-3-ethylene ketal. Moreover it can be dehydrogenated with *N. aurantia* as described in Example 28 for the corresponding 6α-chloro compound.

6β,9α - Difluoro - pregnane - 5α,11β,16α,17α,-21 - pentol - 3,20 - dione - 16α,17α-Acetonide 3-Ethylene Ketal

To a solution of 500 mg. of 5α,6α-oxido-9α - fluoro - 16α - hydroxyhydrocortisone-16α,17α-acetonide 3-ethylene ketal in 60 ml. of dry benzene and 15 ml. of absolute ether is added 1 ml. of freshly redistilled boron trifluoride etherate and the solution allowed to remain at room temperature for three hours. After thorough washing with water the organic phase is dried over sodium sulfate and the solvents removed *in vacuo*. Recrystallization from acetone-hexane gives the pure 6β-fluorohydrin, which is further treated as in Example 27 to form 6α,9α-difluoro-16α-hydroxycortisone-16α,17α-acetonide.

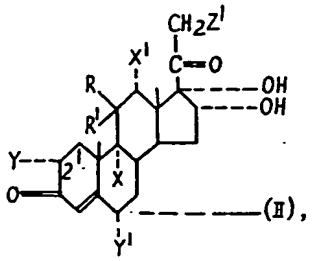
WHAT WE CLAIM IS:—

1. A process for preparing a steroid of the general formula:



(I),

in which the 1- and 2- positions are saturated or linked by a double bond; R is hydrogen, R^1 is β-hydroxy or R and R^1 together constitute a keto group; X is hydrogen, halogen, hydroxy, lower alkyl or lower alkoxy; X^1 is hydrogen or lower alkyl; Y is hydrogen or methyl; Y^1 is halogen; Z is hydrogen, hydroxy or acyloxy; P and Q are hydrogen, lower alkyl, halogenated lower alkyl, monocyclic cycloalkyl, monocyclic aryl, monocyclic aryl lower alkyl, monocyclic heterocyclic, or monocyclic heterocyclic lower alkyl; or, together with the carbon atom to which they are joined, P and Q form a cycloalkyl or monocyclic heterocyclic group, in which process a steroid of the general formula:



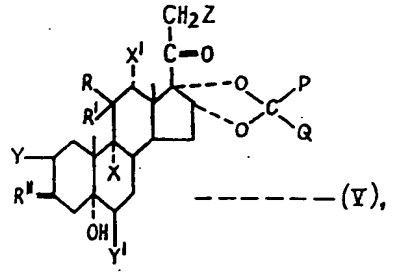
(II),

in which the 1- and 2- positions are saturated or linked by a double bond; R, R^1, X, X^1, Y and Y^1 are as hereinbefore defined; and Z^1

is hydrogen or hydroxy, is reacted with a compound of the formula: $>C=O$, in which P and Q are as hereinbefore defined, and, if desired, the 21-hydroxy position is acylated with an acyl halide or an acid anhydride.

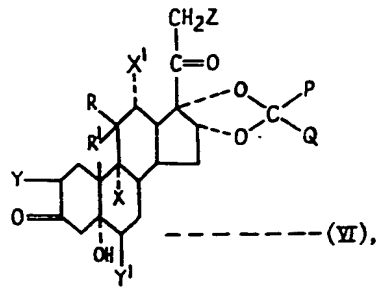
2. A process as claimed in Claim 1 in which the reaction is carried out by treating a suspension of the steroid (II) in the aldehyde or ketone with an acid catalyst, neutralizing the acid and recovering the acetal or ketal derivative formed.

3. A process for preparing a steroid of the general formula (I) defined in Claim 1, the 1- and 2- positions being saturated, in which process a steroid of the general formula:



(V),

in which Y^1 is halogen, R is hydrogen, R^1 is β-hydroxy or together R and R^1 constitute a keto group; X is hydrogen, halogen, hydroxy, lower alkyl or lower alkoxy; X^1 is hydrogen or lower alkyl; Y is hydrogen or methyl; R^{11} is -O-(lower alkylene)-O- or two lower alkoxy radicals; Z is hydrogen, hydroxy or acyloxy; P and Q are hydrogen, lower alkyl, halogenated lower alkyl, monocyclic cycloalkyl, monocyclic aryl, monocyclic aryl, lower alkyl, monocyclic heterocyclic, or monocyclic heterocyclic lower alkyl; or, together with the carbon atom to which they are joined, P and Q form a cycloalkyl or monocyclic heterocyclic group, or of the general formula:



(VI),

in which R is hydrogen, R^1 is β-hydroxy, or, R and R^1 together constitute a keto group; X is hydrogen, halogen, hydroxy, lower alkyl or lower alkoxy; X^1 is hydrogen or lower alkyl; Y is hydrogen or methyl; Y^1 is halogen, Z is hydrogen, hydroxy or acyloxy; P and Q are hydrogen, lower alkyl, halogenated lower alkyl, monocyclic monoalkyl, monocyclic aryl, monocyclic aryl lower alkyl, monocyclic heterocyclic or monocyclic heterocyclic lower alkyl; or, together with the carbon atom to which they are joined, P and Q form a cycloalkyl or monocyclic heterocyclic group, is treated with a strong inorganic acid.

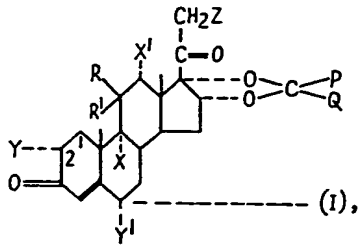
4. A process as claimed in Claim 3 in which the strong inorganic acid is perchloric acid.

5. A process as claimed in Claim 3 in which the strong inorganic acid is hydrochloric acid.

6. A process as claimed in any of Claims 3 to 5 in which the strong inorganic acid is used in glacial acetic acid.

7. A process as claimed in any of Claims 3 to 6 in which a free 21-hydroxy group is esterified by treatment with an acyl halide or acid anhydride.

8. A steroid of the general formula:



(I),

in which the 1- and 2- positions are saturated or linked by a double bond; R is hydrogen, R^1 is β-hydroxy, or R and R^1 together constitute a keto group; X is hydrogen, halogen, hydroxy, lower alkyl or lower alkoxy; X^1 is hydrogen or lower alkyl; Y is hydrogen or methyl; Y^1 is halogen; Z is hydrogen, hydroxy or acyloxy; P and Q are hydrogen, lower alkyl, halogenated lower alkyl, monocyclic cycloalkyl, monocyclic aryl, monocyclic aryl lower alkyl, monocyclic heterocyclic or monocyclic heterocyclic lower alkyl; or, together with the carbon atom to which they are joined, P and Q form a cycloalkyl or monocyclic heterocyclic group.

9. 16α.17α - (Lower alkylidene) - 6α,9α-dihalo-16α-hydroxyhydrocortisone.

10. 16α,17α - (Lower alkylidene) - 6α,9α-dihalo-16α-hydroxy-prednisolone.

11. 16α,17α-(Lower haloalkylidene)-6α,9α-dihalo-16α-hydroxy-prednisolone.

12. 16α,17α - (Lower alkylidene) - 6α-halo - 9α - (lower alkyl) - 16α - hydroxy-prednisolone.

13. 16α,17α - (Lower alkylidene) - 6α,9α-dihalo - 12α - (lower alkyl) - 16α - hydroxy-hydrocortisone.

14. A process for preparing a steroid of the

general formula (I) defined in Claim 1 substantially as hereinbefore described with reference to any of the specific Examples.

15. Steroids of the general formula (I) defined in Claim 1 whenever prepared by a process as claimed in any of Claims 1 to 7 and 14.

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